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Title: The risk of mortality following secondary fundoplication in a population-based cohort study

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Introduction

Fundoplication is an effective and safe treatment option of severe gastroesophageal reflux disease, especially among young and physically fit patients.(1, 2) Our recently published population-based study of 8947 patients who underwent primary laparoscopic fundoplication in Sweden at the age of 18-65 years found an all-cause 90-day mortality of 0.08% (7 patients) and only 1 (0.01%) directly surgery-related death.(2) However, despite initial successful initial results, many patients get recurrent symptoms of reflux and need to undergo a secondary fundoplication. A recent assessment of 13,050 patients undergoing primary laparoscopic fundoplication in the United States, determined that 5.2% and 6.9% of the patients underwent secondary fundoplication within 5 years and 10 years, respectively.(3) Since secondary fundoplication is generally more technically demanding and more time-consuming than primary fundoplication, there is a belief that such surgery entails higher risk of severe complications, including mortality. Yet, the risk of mortality following secondary fundoplication has been scarcely studied. A recent population-based study in Denmark, including 113 patients undergoing secondary fundoplication, found a higher rate of conversion, longer hospital stay and a slightly higher 30-day postoperative mortality rate following secondary fundoplication, compared to primary fundoplication (0.81% versus 0.45%).(4) A systematic review of 20 studies, including a total of 930 patients having undergone secondary fundoplication, found only 2 perioperative deaths (0.22%).(5) The main aim of the present study was to estimate the risk of mortality within 90 days of secondary fundoplication using a population-based design, thus providing an unselected cohort.

Materials and methods

The design of the nationwide Swedish cohort of patients aged 18-65 years who underwent primary laparoscopic fundoplication for gastroesophageal reflux diagnosis in 1997-2013 has been described elsewhere.(2) The present study was also a nationwide Swedish population-based cohort study during

the same time period, but it only included patients who had undergone secondary fundoplication (open or laparoscopic) after primary laparoscopic fundoplication, without any upper age limit and regardless of indication. The patients were identified using the Swedish Patient Registry, which records all in-hospital care in Sweden since 1987, and includes data on diagnoses, procedures, demography, and hospitalization dates.(6)

The currently used version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures was introduced in the Patient Registry in 1997, which enables identification of laparoscopic and open surgical procedures separately, hence determining the start date of the study. The surgical procedures were identified using the surgical procedure codes 'JBC01' and 'JBC00', for laparoscopic and open fundoplication, respectively. The primary outcome was 90-day postoperative mortality, which is recommended in assessing postoperative mortality following upper gastrointestinal surgery.(7) Date and causes of death were retrieved from the Swedish Causes of Death Registry, which is 100% complete regarding date of death and 99.2% complete regarding main cause of death.(8) The secondary outcome was length of hospital-stay. Data from each study participant were linked using the individual 10-digit personal identity number, which is assigned to each Swedish resident upon birth or immigration, and has been validated as an effective tool for research purposes.(9) The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (reference number 2014/234-31).

Results

Among 9,765 patients who had undergone primary laparoscopic fundoplication at the age of 18 years or later, 540 patients (5.5%) underwent a secondary fundoplication with an equal number of men and women (Table 1). There were no deaths within 90 days of secondary fundoplication. Of the secondary fundoplications, 382 were laparoscopic (70.7%) and 158 were open (29.3%). The mean length of hospital

stay was longer following secondary fundoplication (4.8 days, interquartile range 1.0-5.0) compared to primary fundoplication (2.5 days, interquartile range 1.0-3.0).

Discussion

This study found no deaths within 90 days of secondary fundoplication in 540 patients. The hospital stay following secondary fundoplication was longer compared to primary fundoplication, and nearly one third were conducted using an open surgical approach.

Among strengths of the study is the population-based design, which counteracts selection bias, the reliability of the registry data with complete coverage of surgical procedures and mortality, and the large size of the cohort. Due to the study design, based on data from national registries, the cohort reflects the outcome of all surgeries conducted in Sweden, and not limited only to specialized centers. Among weaknesses is the limited number of patients having undergone secondary fundoplication and the inability to assess the conversion rate from laparoscopic to open approach. However, the latter was not the aim of the study. Another weakness is the lack of data regarding clinical follow-up in the registers, such as quality of life or reflux symptom scores, thereby limiting conclusions regarding clinical improvement following surgery.

This study shows an even lower mortality rate than the two recent investigations examining the same topic. A population-based Danish study found a 30-day mortality rate of 0.81% (n=1) following secondary fundoplication among 124 patients.⁽⁴⁾ A systematic review including 930 secondary fundoplications from 20 studies found 2 postoperative deaths (0.2%),⁽⁵⁾ both deaths occurring in one study of 76 patients.⁽¹⁰⁾

There are several potential explanations for the low short-term mortality following secondary fundoplication. Recent decades have witnessed a reduction in fundoplication.(2) This reduction has led to a centralization of services to fewer surgeons with a special interest and experience in selecting suitable patients and in performing fundoplication of high quality, which should lower the risk of mortality following secondary fundoplication. In such high-volume centers, minimally invasive surgery is usually a successful approach for secondary fundoplication, and the need for open surgery is limited. Another factor that might contribute to these encouraging results is that laparoscopic fundoplication entails less scarring, fibrosis or adhesions in the operation field compared to open surgery.(11) Thus, secondary fundoplication might be less complex in an era where laparoscopy is the dominating approach for primary fundoplication. Finally, the development of postoperative care and advances in laparoscopic techniques during recent decades might contribute to explain the low mortality rates.

Secondary fundoplication has been reported to be required in approximately 5% of patients during the first five years following primary fundoplication.(3, 4) The findings of such low reoperation rates are in line with our population-based results, where the overall secondary fundoplication rate was only 5.5%. The longer hospital stay following secondary fundoplication was likely explained mainly by the fact that nearly one third had open surgery.

In conclusion, this population-based and nationwide Swedish cohort study indicates that secondary fundoplication is a safe procedure. The longer hospital stay following secondary fundoplication compared to primary fundoplication is likely explained by the higher rate of open procedures.

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Table 1. Outcomes following secondary fundoplication, compared to primary fundoplication.

| | Secondary fundoplication | Primary laparoscopic fundoplication |
|-------------------------------------|--------------------------|-------------------------------------|
| Number of patients | 540 | 9,765 |
| Age, mean (IQR) | 51.3 (42-60) | 48.7 (39-58) |
| Male sex, number (%) | 269 (49.8) | 5,574 (57.1) |
| Laparoscopic technique, number (%) | 382 (70.7) | 9,765 (100.0) |
| Open technique, number (%) | 158 (29.3) | N/A |
| Mortality rate, number (%) | 0 (0.0) | N/A |
| Length of hospital-stay, mean (IQR) | 4.8 (1.0-5.0) | 2.5 (1.0-3.0) |

IQR: Interquartile range, N/A: Not applicable